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[54] **PREVENTING CONVERSION OF CITRULLINE TO ARGININOSUCCINATE TO LIMIT PATHOLOGICAL NITRIC OXIDE OVERPRODUCTION**

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[56] References Cited

U.S. PATENT DOCUMENTS

4,775,623	10/1988	Katsumata et al.	435/114
5,028,627	7/1991	Kilbourn et al.	514/565
5,059,712	10/1991	Griffith	562/560
5,196,195	3/1993	Griffith et al.	424/94.6
5,216,025	6/1993	Gross et al.	514/565
5,364,881	11/1994	Griffith et al.	514/508
5,424,447	6/1995	Griffith et al.	594/74
5,464,858	11/1995	Griffith et al.	514/399

FOREIGN PATENT DOCUMENTS

WO95/01972 1/1995 WIPO .

OTHER PUBLICATIONS

- Carignan, J. A., et al, Hosp. Formul. 21, 1025-1030 and 1033 (1986).
Corbett, J. A., et al, J. Clin. Invest. 90, 2384-2391 (1992).
Jinno, Y., et al, EMBL Database, Sequence from J. Biochem. 98, 1395-1403 (1985).
Kleeman, R., et al, FEBS, 328, 9-12 (Aug. 1993).
Nussler, A. K. et al, J. Biol. Chem., 269, 1257-1261 (1994).
Schmidt, H. H. H. W., et al, Eur. J. Pharmacol., 148, 293-295 (1988).
Corbett, J. A., et al, Proc. Natl. Acad. Sci. USA, 90, 1731-1735 (Mar. 1993).
Corbett, J. A., et al, Proc. Natl. Acad. Sci. USA, 90, 8992-8995 (Oct. 1993).
Kroncke, K-D, et al, Biochem. Biophys. Res. Commun. 175, 752-758 (1991).
Lukic, M. L., et al, Biochem. Biophys. Res. Commun. 178, 913-920 (1991).

Schmidt, H. H. H. W., et al, Eur. J. Pharmacol., 154, 213-216 (1988).
Sessa, W. C., et al, Proc. Natl. Acad. Sci. USA, 87, 8607-8611 (Nov. 1990).

Corbett, J. A., et al, Biochemistry 32, 13767-13770 (1993).

Cross, A. H., et al, J. Clin. Invest. 93, 2684-2690 (1994).

McCartney-Francis, N., et al, J. Exp. Med. 178, 749-754 (1993).

Misko, T. P., et al, Eur. J. Pharmacol. 233, 119-125 (1993).

Suarez-Pinzon, W. L., et al, Endocrinology, 134, 1006-1010 (1994).

Takada, S., et al, J. Biochem. 85, 1309-1314 (1979).

Freytag, S. O., Medline Abstract of J. Biol. Chem., 259, 3160-6 (1984).

Grisolia, S., et al, The Urea Cycle, John Wiley & Sons, p. 191 (1976).

Mitchell, J. A., et al, Eur. J. Pharmacol., 182, 573-576 (1990).

Mulligan, M. S., et al, Proc. Natl. Acad. Sci. USA, 88, 6338-6342 (Jul. 1991).

Weinberg, J. B., et al, J. Exp. Med. 148, 651-660 (Feb. 1994).

Wu, G., et al, Biochem. J., 281, 45-48 (1992).

Hattori, Y., et al, J. Biol. Chem. 269, 9405-9408 (1994).

Ialenti, A., et al, Eur. J. Pharmacol. 211, 177-182 (1992).

Mulligan, M. S., et al, Br. J. Pharmacol., 107, 1159-1162 (1992).

Nathan, C. F., et al, Current Opinion in Immunology, 3, 65-70 (1991).

Yang, X., et al, J. Clin. Invest., 94, 714-721 (1994).

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[57] ABSTRACT

Administration of argininosuccinate synthetase activity reducing agents, e.g., argininosuccinate synthetase induction blocking agents (e.g., antibiotics that bind to DNA sequences present in the upstream regulatory region of the argininosuccinate synthetase gene, such as mithramycin) and argininosuccinate synthetase inhibitors (e.g., L-citrulline antagonists such as methyl citrulline and L-aspartate antagonists such as D-aspartate) is useful to prevent or treat sepsis or cytokine-induced systemic hypotension, is useful in the treatment of sepsis or cytokine-induced systemic hypotension to restore vascular sensitivity to the effects of α_1 -adrenergic agonists, and is useful to suppress an immune response, e.g., in treating inflammation. In one embodiment, certain argininosuccinate synthetase activity reducing agents are used together with arginine antagonists to treat sepsis or cytokine induced hypotension.